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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
CROUCH, D	
ART UNIT	**PAPER NUMBER**
1632	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/226,766	Wangh
Examiner	**Group Art Unit**
Deborah Crouch	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *87-156* is/are pending in the applicat

Of the above, claim(s) *142-156* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *87-141* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 87-141, drawn to in methods of transplantation of a donor cell nucleus other than a sperm or egg nucleus into a recipient egg, an improvement comprising incubating said donor cell nucleus in cytoplasms consisting of two types: first a cytostatic factor -containing cytoplasm that is arrested in metaphase II or mitotic metaphase; and second in activated egg cytoplasm, classified in class 800, subclass 24.

II. Claims 142-156, drawn to methods for activating a nucleus of an animal cell in vitro, classified in class 435, subclass 2, 6, 375 and 377.

The inventions are distinct, each from the other because:

Invention I is to an in vivo method of cloning by nuclear transfer, where a donor nucleus is inserted into an egg such that a viable term animal, genotypically identical to the donor nucleus, is produced. Invention II is to an in vitro method of causing cells to enter into a cell division stage that makes their chromosomes more readily available for in vitro assays. The inventions are distinct because the method of cloning of invention I requires in vivo protocols and procedures that are above and beyond those in vitro protocols and procedures of invention II. The method of cloning of invention I is, additionally, a different use of the methods of activation of invention II. The specification discloses that the method can be used to activation sperm cells and fetal red blood cells. For these reasons inventions I and II are patentably distinct.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Stuart MacPhail on May 19, 2000 a provisional election was made with traverse to prosecute the invention of group I, claims 87-141. Affirmation of this election must be made by applicant in replying to this Office action. Claims 142-152 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87-141 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 87-141 are drawn to the transplantation of a donor cell nucleus other than a sperm or egg nucleus into a recipient egg for the purpose of cloning, comprising an improvement where the donor-cell nucleus in incubated in cytoplasms consisting of two types 1) in a cytostatic factor-containing cytoplasm that is arrested in meiotic metaphase II or mitotic metaphase, and 2) in activated egg cytoplasm. Dependent claims address various limitations to this method, or methods implied but not stated in this method.

The claims are not enabled as there is not evidence of record that the method would permit sufficient reprogramming of the donor nucleus that a viable term organism would be produced. The claimed method is a method of cloning where the donor nucleus is incubated with two separate egg cytoplasms such that the incubation is to cause the donor nucleus to "reprogram", that is revert back to totipotent state as is a fertilized egg or an early embryo, such that the when the so incubated donor-nucleus is then inserted into an egg, development will ensue to produce a full term, viable organism that is genotypically identical to the donor-egg.

The specification offers as an guidance at page 58, line 20 through page 60. At this citation, the specification discusses that the disclosed method of cell activation should provide for a donor nucleus in a nuclear transfer procedure to remove the imprint pattern from the donor nucleus' chromosomes, and thus the donor nucleus will

be reprogrammed and able to provide full development into a term animal. However, the term "should allow for the necessary reprogramming" indicates that there is uncertainty in the method, that the disclosed method for activating cells might not allow for reprogramming. This, in view of the art at the time of filing which indicated that reprogramming and cloning as a whole enterprise is unpredictable without undue experimentation, renders the claims as not enabled.

The art at the time of filing clearly recognized that some outside event to the donor nucleus in a nuclear transfer procedure, as is the disclosed method, must occur for successful develop of the nuclear transfer unit (NT unit) into a live birth of a fully developed, live animal. Both reprogramming and nuclear/nucleoli remodeling are events the art regards as necessary for a cell to be complete totipotential, that is for the cell to become competent to give rise to a live birth. Fulka et al state that the success when embryonic cells were used as nuclei donor was likely due to the embryo cells not being completely differentiated at the time of transfer, and thus amenable to undergo full reprogramming (page 848, col. 1, parag. 1, line 1 to col. 2, line 1). Fulka et al sates that complete genomic reprogramming in transplanted nuclei would be accompanied by a sequence of developmental and biochemical changes in the reconstructed embryo that would exactly parallel those detected in normal embryos after fertilization (page 850, col. 2, parag. 1, lines 7-11). No such parallel has been shown in nuclei activated by the claimed method. Kono states that a break down of the nuclear envelop is necessary for reprogramming, as reprogramming probably requires the contact of the

chromatin with the ooplasm (page 76, col. 2, parag. 2, lines 1-6). There is no evidence of record that the incubation of nuclei with a cytostatic egg extract followed by incubation with an activating egg extract correlates with exposure to the ooplasm. Wolf et al states that the coordination between cell cycles of donor and recipient cell is important to avoid DNA damage and to maintain correct ploidy of the embryo (Wolf, page 102, col. 2, lines 2-5). Wolf also states, and in support of Kono, that a donor nucleus is reprogrammed by the recipient cytoplasm, where the donor nucleus is reverted to the same morphological and temporal pattern of the zygote (Wolf, page 102, col. 1, lines 1-4). There has been no showing by an any means that the incubation steps result in nuclei that by any criteria revert to zygotic morphological or temporal form. It is noted that Fulka et al stated that the cloning of adult mammals is very inefficient and highly unpredictable (page 849, col. 1, lines 9-10 and page 850-851, bridg. sent.). The art also taught that activation of the embryonic genomic, that is the production of embryonic mRNA, occurs at different cell divisions in mammalian embryos, but that reprogramming has to be complete a the time of activation. In mice, reprogramming had to be complete by the second cell division. In cattle sheep activation occurs at the fourth cleavage, and reprogramming is believed to occur slowly over the first or second cell cycles (Fulka et , page 850, parag. 1, lines 16-25). The specification provides no guidance that a reprogramming event would occur prior to activation of the embryonic genome. Thus the art at the time of filing, recognized that the cloning of mammals required a process where the donor nuclei, by a mechanism

that was not clear, were reprogrammed such that the differentiation status of the donor nuclei returned to totipotent. This return to a totipotent state has not been shown to occur when donor nuclei are incubated as claimed. Thus, the specification does not provide guidance to overcome these art recognized needs and unpredictabilities in the claimed methods.

It is noted that the specification discloses methods for activating the nucleus of cells, with specific examples demonstrating results in fetal erythrocytes and sperm. In both fetal erythrocytes and sperm, nuclei were isolated, pretreated with a detergent, incubated in a cytostatic egg extract prepared from non-induced Xenopus eggs arrested in meiotic metaphase, and then incubated in an activating egg extract prepared from Xenopus eggs at their time of highest incorporation of radio-labeled nucleotide post-induction of the cell cycle. The results of this treatment was obtaining fetal erythrocyte and sperm nuclei with condensed chromosomes, that is metaphase chromosomes, in swollen nuclei to enhance the performance of routine nucleic acid analysis or the study of nuclear structures. However, there is no evidence that obtaining of metaphase chromosomes by the method claimed, results in the reprogramming of the cell. The specification never offered any evidence that the fetal erythrocyte nuclei, treated by the claimed method returned the nuclei to a totipotent state. The specification does not disclose the phenotype of the nuclei which were treated and permitted to complete the replication cycle. There is no guidance in either the specification or the art that the return of nuclei to mitotic metaphase results in the reprogramming of nuclei such that

they can support the development of a viable, term animal. The specification further omits guidance to essential steps in the cloning procedure. In particular, there is no guidance as to which meiotic stage egg the treated nuclei will be transferred to complete development. The stage of the egg in meiosis certainly would be critical in maintaining the activation of the donor nucleus such that proper development to a viable, term animal would occur.

The instant invention falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genetech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). While the specification suggests that the claimed method can be used in methods of cloning, there is no evidence in the record or in the art that supplies the guidance needed to enable the cloning of animal by the claimed method. Specific guidance is needed that the activation of nuclei by the claimed method would return them to the totipotent state needed to create a complete, new animal.

Thus, for the reasons given above, the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed as there is insufficient guidance in the specification,

in view of the state of the art at the time of filing, that the claimed methods would result in nuclear reprogramming sufficient to produce by nuclear transfer a viable, term animal.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 87-141 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are written in Jepson format, which of course is acceptable by the Patent Office. However, the use of the Jepson format is confusing, as methods of cloning are not broadly accepted as enabled by the art. It would be clearer if the claims were to be written in regular format clearly stating at which step of the known methods is the claimed method to be inserted.

The claims are free of the prior art. At the time of filing, the prior art did not teach or suggest methods of nuclear transfer, where the donor nucleus was incubated first in a cytostatic egg extract and second in an activating egg extract.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. D. Crouch
May 21, 2000